



DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:

Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500, MSC 6910
Bethesda, Maryland 20892-6910
Home Page: <http://grants.nih.gov/grants/olaw/olaw.htm>

FOR EXPRESS MAIL:

Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500
Bethesda, Maryland 20817
Telephone: (301) 496-7163
Facsimile: (301) 402-7065

March 15, 2019

Re: Animal Welfare Assurance
A3001-01 [OLAW Case O]

John A. Zaia, M.D.
Deputy Director for Clinical Research
City of Hope National Medical Center/Beckman Research Institute
1500 East Duarte Road
Duarte, CA 91010-3000

Dear Dr. Zaia,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your March 8, 2019 letter reporting an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at the City of Hope National Medical Center- Beckman Research Institute. According to the information provided, OLAW understands that 24 mice received two different injectable experimental drugs not listed on the approved protocol. Thirteen of the mice receiving one drug subsequently died and the remainder were euthanized. Additional mice were injected with another unapproved drug before the protocol amendment had been approved.

The corrective actions consisted of the Institutional Animal Care and Use Committee (IACUC) directing the Principal Investigator to submit a protocol amendment to add the drugs, to submit an unanticipated problem report, and to stop any unapproved animal activities. The amendment described a lower concentration of one drug and lower frequency of administration and was subsequently approved by the IACUC. Up to date versions of the protocol will be maintained in the laboratory's electronic shared folder and staff must review this before starting new animal activities. Designated laboratory staff will ensure that these procedures are followed and will train new staff. All laboratory staff was trained on the electronic protocol submission system and on safely using the hazardous drugs. The NIH grant was not charged for any unauthorized animal activities and the funding component was notified.

Based on its assessment of this explanation, OLAW understands that measures have been implemented to correct and prevent recurrence of this problem. OLAW concurs with the actions taken by the IACUC to comply with the PHS Policy.

Sincerely,

(b) (6)

Axel Wolff, M.S., D.V.M.
Deputy Director
Office of Laboratory Animal Welfare

cc: IACUC Contact

March 8, 2019

Division of Compliance Oversight
Office of Laboratory Animal Welfare
OLAW Division of Assurance
National Institutes of Health
Suite 360 MSC 7982
6705 Rockledge Dr.
Bethesda, MD 20817

To Whom It May Concern,

City of Hope National Medical Center – Beckman Research Institute (“City of Hope”), in accordance with Assurance A3001-01 and PHS Policy IV.F.3, provides this report of noncompliance regarding administration of two drugs – Decitabine and N-Nitroso-N-ethylurea (ENU) – to mice, an activity not reviewed and approved by the City of Hope IACUC in a Principal Investigator’s (PI) animal use protocol entitled “*Genetic and Epigenetic Studies in Cancers*” (the “Protocol”). The procedures performed on these animals involved federal funds from NIH Grants R01CA214965 and R56DK120282.

Incident Description:

On December 13, 2018, 24 mice were injected with Decitabine, a drug that was not listed on the approved Protocol. Between December 14, 2018 and December 21, 2018, 13 of the mice that were injected were found dead and 2 of the mice that were injected were euthanized due to poor condition. All remaining mice (n=9) were euthanized as of January 5, 2019.

On December 21, 2018, the IACUC Executive Committee (EC) met to discuss the issue and the PI was informed that use of Decitabine may not resume until this work has been approved by the IACUC. The PI was asked to submit an amendment to the approved Protocol to add Decitabine as well as submit an unanticipated problem report describing the unanticipated deaths. The unanticipated problem report was submitted on December 21, 2018 and the amendment was submitted on January 2, 2019. In addition to Decitabine, the amendment also added several other drugs to the Protocol, including N-Nitroso-N-ethylurea (ENU).

On January 18, 2019, the IACUC EC was informed by City of Hope’s Center for Comparative Medicine (CCM) staff and Biosafety Officer that the laboratory administered ENU to mice. The amendment submitted on January 2, 2019 to add this drug had not yet been approved at the time of the drug administration.

On January 24, 2019, a letter was sent from the IACUC EC to the PI indicating that work with ENU must immediately stop and a corrective action plan must be submitted to prevent similar situations from occurring in the future. That same day, the PI responded with a proposed corrective action plan.

On February 5, 2019, the IACUC Full Committee reviewed the case and voted to classify this as a serious noncompliance as it created a condition resulting in actual harm to animals. The final corrective action plan is included below.

Corrective Action Plan:

- To address the unanticipated deaths, the laboratory lowered the concentration of Decitabine and reduced the frequency of administration in the amendment submitted on January 2, 2019. The amendment was approved by the IACUC on February 18, 2019.
- To correct the problem of laboratory staff not knowing when a new version of the Protocol has been approved and to better facilitate staff access to the current version, the Protocol will be saved in the laboratory's electronic shared folder and will be replaced with a new version each time the Protocol is amended or renewed. All lab members will be required to review the current approved version of the Protocol. Prior to initiating any new experiments, lab members will re-review the current approved version of the Protocol to ensure all work is covered. No new experiments will be conducted until the relevant amendment to the Protocol has been approved by the IACUC. The PI designated several individuals in the laboratory who are responsible for ensuring that all lab members follow this process. Additionally, the PI will continue to emphasize this process during regular laboratory meetings.
- The PI designated several individuals from the laboratory who are responsible for training new lab members, emphasizing during this training the importance of protocol adherence.
- All lab members must complete training on using the electronic protocol submission system. Training was completed on March 1, 2019.
- All lab members who will work with Decitabine and ENU must go through training with the Safety Office, to include training on carcinogen and mutagen use. Training was completed on February 19, 2019.

In addition to the corrective action plan noted above, all expenses charged to the NIH grants related to the unapproved work were transferred to a non-sponsored source and the NIH funding agency was notified of the situation.

Please be assured that City of Hope takes this matter very seriously and remains committed to full compliance with the federal and state regulations and requirements.

We believe this letter fulfills our reporting obligations; however, please contact me at (b) (6) if you have any questions or require additional information.

Sincerely,

(b) (6)

John A. Zaia, MD
Institutional Official

cc: Nadia Carlesso, M.D., Chair, Institutional Animal Care and Use Committee
Richard W. Ermel, D.V.M., M.P.V.M., Ph.D., DACLAM, Attending Veterinarian
Alyse DiStefano, Director, Laboratory Research Protections
(b) (6)

Jaclyn Lucas, Director, Office of Sponsored Research

Morse, Brent (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Tuesday, March 12, 2019 7:55 AM
To: DiStefano, Alyse; OLAW Division of Compliance Oversight (NIH/OD)
Cc: Zaia, John; Carlesso, Nadia; Ermel, Richard; (b) (6)
(b) (6) Lucas, Jaclyn
Subject: RE: Report of Noncompliance

Thank you for providing this report. We will send an official response soon.

Best regards, Brent Morse

Brent C. Morse, DVM, DACLAM
Director
Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

Please note that this message and any of its attachments are intended for the named recipient(s) only and may contain confidential, protected or privileged information that should not be distributed to unauthorized individuals. If you have received this message in error, please contact the sender.

From: DiStefano, Alyse [mailto:adistefano@coh.org]
Sent: Monday, March 11, 2019 7:32 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: Zaia, John <JZaia@coh.org>; Carlesso, Nadia <ncarlesso@coh.org>; Ermel, Richard <RErmel@coh.org>; (b) (6)
(b) (6) Lucas, Jaclyn
<jalucas@coh.org>
Subject: Report of Noncompliance

To Whom It May Concern,

Attached please find a report of noncompliance for your review.

Please let me know if you have any questions.

Thank you,

(b) (6)



***SECURITY/CONFIDENTIALITY WARNING:**

This message and any attachments are intended solely for the individual or entity to which they are addressed. This communication may contain information that is privileged, confidential, or exempt from disclosure under applicable law (e.g., personal health information, research data, financial information). Because this e-mail has been sent without encryption, individuals other than the intended recipient may be able to view the information, forward it to others or tamper with the information without the knowledge or consent of the sender. If you are not the intended recipient, or the employee or person responsible for delivering the message to the intended recipient, any dissemination, distribution or copying of the communication is strictly prohibited. If you received the communication in error, please notify the sender immediately by replying to this message and deleting the message and any accompanying files from your system. If, due to the security risks, you do not wish to receive further communications via e-mail, please reply to this message and inform the sender that you do not wish to receive further e-mail from the sender. (LCP301)